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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

HELSINN HEALTHCARE S.A. and  
ROCHE PALO ALTO LLC,

Plaintiffs,

v.

DR. REDDY'S LABORATORIES, LTD.,  
DR. REDDY'S LABORATORIES, INC.,  
SANDOZ, INC., TEVA PHARMACEUTICALS  
USA, INC., and TEVA PHARMACEUTICAL  
INDUSTRIES, LTD.,

Defendants.

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)  
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)  
) Civil Action No. 11-3962 (MLC)(DEA)  
) Civil Action No. 11-5579 (MLC)(DEA)  
) (consolidated)  
)  
) Hon. Mary L. Cooper, U.S.D.J.  
) Hon. Douglas E. Arpert, U.S.M.J.  
)  
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)

**DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF**

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## INTRODUCTION

This patent litigation involves three asserted patents: U.S. Patent Nos. 7,947,724 (the “‘724 patent”), 7,947,725 (the “‘725 patent”), and 7,960,424 (the “‘424 patent”) (collectively, the “asserted patents”). The claims of the asserted patents are directed to pharmaceutically stable intravenous palonosetron formulations that can be used for reducing or reducing the likelihood of emesis.<sup>1</sup> Plaintiffs Helsinn Healthcare S.A. and Roche Palo Alto LLC (collectively, “Helsinn” or “Plaintiffs”) are asserting claims 1-7 and 9 of the ‘724 patent, claims 1 and 2 of the ‘725 patent, and claims 1-6 of the ‘424 patent against Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively, “Teva”) and Defendants Sandoz, Inc. (“Sandoz”); and are asserting claims 1-4 and 9 of the ‘724 patent, claims 1 and 2 of the ‘725 patent, and claims 1-3, 5, and 6 of the ‘424 patent against Defendants Dr. Reddy’s Laboratories, Ltd. and Dr. Reddy’s Laboratories, Inc. (collectively, “DRL”) (all collectively, “Defendants”).

The only claim term in dispute is “pharmaceutically stable.” This term appears in each of the asserted claims. Defendants’ construction, *i.e.* “without significant change in chemical and physical integrity for pharmaceutical use,” is the plain and ordinary meaning of “pharmaceutically stable,” and is supported by both intrinsic and extrinsic evidence. Ex. 1, Joint Claim Construction and Prehearing Statement at 3.<sup>2</sup> While Plaintiffs contend that their construction, *i.e.*, “shelf stable for periods greater than 24 months at room temperature” (*id.*), is the “plain and ordinary meaning” of the claim term, the evidence directly refutes that position. Specifically, the intrinsic record shows that Plaintiffs are trying to use this claim construction proceeding to rewrite the claims by importing limitations (*e.g.*, “shelf stable,” “24 months,” and “room temperature”) into the claims when during prosecution similar limitations were added to

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<sup>1</sup> Emesis, *i.e.*, vomiting, is a side-effect of chemotherapy, radiotherapy and post-operative environments. Ex. 2, ‘724 patent at col. 1, ll. 15-17.

<sup>2</sup> “Ex. \_\_\_” refers to the exhibits annexed to the Declaration of Jovial Wong filed with this brief.

the claims but later deleted by the inventors after the claims were rejected over the prior art. Under such circumstances, Defendants' construction should be adopted.

## **I. FACTUAL BACKGROUND**

### **A. Drug Formulation Background**

Palonosetron belongs to a class of drugs commonly known as 5-HT<sub>3</sub> (5-hydroxytryptamine) receptor antagonists, which are effective in treating emesis. As such, these drugs are also referred to as anti-emetics. Ex. 2, '724 patent at col. 1, ll. 15-33.<sup>3</sup> Other 5-HT<sub>3</sub> receptor antagonists that were known and/or marketed prior to palonosetron include ondansetron, granisetron, tropisetron, and dolesetron. All of these drugs were typically administered intravenously to control the emesis effects of chemotherapy. *Id.*

Plaintiffs did not discover palonosetron. Nor were they the first to discover that it had anti-emetic properties and that it could be administered intravenously like other 5-HT<sub>3</sub> receptor antagonists. All of those discoveries were made by others at least a decade before the earliest filing date of the asserted patents in 2003. Specifically, the inventors of U.S. Patent No. 5,202,333 to Berger *et al.* (the "'333 patent") disclosed that palonosetron was more effective and more potent in reducing emesis than other prior art 5-HT<sub>3</sub> receptor antagonists. *Id.* at col. 1, l. 46 – col. 2, l. 3. The '333 patent also disclosed therapeutically effective amounts of palonosetron and that a preferred route of administration was by intravenous injection, *and taught* a pharmaceutically stable intravenous palonosetron formulation. *Id.*

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<sup>3</sup> Because all of the asserted patents share the same specification and similar submissions during prosecution, references to the specification and prosecution of the asserted patents will be made with respect to the '724 patent, unless otherwise noted.

## B. The Asserted Patents<sup>4</sup>

After describing what they perceived as problems with prior art 5-HT<sub>3</sub> receptor antagonists, the inventors stated in the specification of the asserted patents that “there exists a need for a palonosetron formulation with increased stability *and* thereby increased shelf life.” *Id.* at col. 2, ll. 36-37 (emphasis added). Then in the Summary of the Invention, the inventors claimed to “have made a series of discoveries” that resulted in palonosetron formulations with increased stability: (1) using less active ingredient (*i.e.* palonosetron) compared to amounts required for prior art 5-HT<sub>3</sub> receptor antagonists; (2) adjusting the pH and excipient concentrations of the formulations; and (3) adding mannitol and a chelating agent in various concentrations. *Id.* at col. 1, l. 56 – col. 3, l. 30. The inventors also claimed to have discovered that their palonosetron formulations can be “stored for prolonged periods of time” at various temperatures, including being “shelf stable for periods greater than 24 months at room temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.” *Id.* at col. 2, ll. 56-62.

As is typical with patent applications, the inventors originally filed various claims to capture the different aspects and embodiments of their inventions. Notably, they chose to claim their invention in terms of “pharmaceutically stable” formulations of palonosetron with specific excipients and palonosetron concentrations. Ex. 5, ‘311 application at 15-20. They did not originally file any formulation claims to encompass the “shelf stable for up to 24 months at room temperature” embodiment of their invention. The inventors later amended the claims (and added

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<sup>4</sup> All of the asserted patents claim priority back to U.S. Provisional Application No. 60/444,351, which was filed in January 2003. The asserted patents were then filed sequentially as a series of continuation patent applications: the ‘724 patent was filed on July 21, 2005 as U.S. Application No. 11/186,311 (the “‘311 application”) (*see* Ex. 2, ‘724 patent at cover); the ‘725 patent was filed on March 24, 2006 as U.S. Application No. 11/368,268 (the “‘268 application”) (*see* Ex. 3, ‘725 patent at cover); and the ‘424 patent was filed on March 24, 2006 as U.S. Application No. 11/388,270 (the “‘270 application”) (*see* Ex. 4, ‘424 patent at cover).

new claims) to expressly cover “pharmaceutically stable” formulations having a shelf stability of greater than 24 months at room temperature, the exact construction being advocated by Plaintiffs in these proceedings. Ex. 6, February 26, 2007 Amendment at 3-10. The Examiner repeatedly rejected the claims with the shelf stability limitations. *See, e.g.*, Ex. 7, October 5, 2007 Office Action and Ex. 8, October 6, 2008 Office Action. In response, the inventors deleted the shelf stability limitations from the pending claims. Ex. 9, April 6, 2009 Amendment at 3-4. Unable to get claims with a shelf stability limitation of any kind, the inventors instead shifted their focus to arguing that the amended claims were patentable over the prior art because of the alleged novelty of the recited excipients and excipient concentrations. *Id.* at 5-9. The inventors also briefed these new arguments in an Appeal Brief, before the claims of the asserted patents were allowed. Ex. 10, May 24, 2010 Appeal Brief.<sup>5</sup> None of the issued claims included limitations to a particular shelf-life stability or temperature condition, as Plaintiffs now advocate, and Plaintiffs should now be held to the previous representations made by the inventors during prosecution. As such, “pharmaceutically stable” cannot mean “shelf stable for periods greater than 24 months at room temperature.”

## II. LEGAL PRINCIPLES FOR CLAIM CONSTRUCTION

As this Court is well aware, claim construction is a pure question of law. *Markman v. Westview Instruments Inc.*, 52 F.3d 967, 970-71, 978 (Fed. Cir. 1995) (*en banc*); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1455-56 (Fed. Cir. 1998) (*en banc*). In *Phillips v. AWH Corp.*, the Federal Circuit confirmed that claim terms should be given “their ordinary and customary meaning;” that is, “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed.

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<sup>5</sup> *See also* Ex. 11, December 15, 2009 Amendment at 4-16 and Ex. 12, October 11, 2010 Appeal Brief at 3-29 in ‘268 Application; Ex. 13, April 29, 2009 Amendment at 2-7 and Ex. 14, November 13, 2009 Appeal Brief at 2-23 in ‘270 Application.

Cir. 2005) (*en banc*). In particular, where the patent specification does not expressly define the claim terms, courts should give the claim terms their plain and ordinary meaning. *See Symantec Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279, 1291 (Fed. Cir. 2008) (it is appropriate to apply the plain and ordinary meaning to claim terms when those terms are not expressly defined in the patent).

The Federal Circuit has stressed the importance of the intrinsic record – the claim language, the specification, and the prosecution history – when construing claim terms. *Phillips*, 415 F.3d at 1317. “Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification.” *Id.* at 1313. Under *Phillips* and its progeny, the patentee “is not entitled to a claim construction divorced from the context of the written description and prosecution history.” *Nystrom v. Trex Co., Inc.*, 424 F.3d 1136, 1144-45 (Fed. Cir. 2005). The intrinsic evidence, therefore, controls the claim construction inquiry.

Claim construction begins by looking at the claim language itself. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (“[t]he starting point for any claim construction must be the claims themselves.”). Along with the claims, the specification tends to provide “dispositive” guidance because “it is the single best guide to the meaning of a disputed term.” *Nice Sys., Inc. v. Witness Sys., Inc.*, 528 F. Supp. 2d 470, 474 (D. Del. 2007) (quoting *Phillips*, 415 F.3d at 1315). Also, “like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.” *Phillips*, 415 F.3d at 1316. Indeed, “the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise

be.’” *Regents of the Univ. of Cal. v. DakoCytomation Cal., Inc.*, 517 F.3d 1364, 1372 (Fed. Cir. 2008) (quoting *Phillips*, 415 F.3d at 1317).

While the Federal Circuit has emphasized the importance of intrinsic evidence in claim construction, it has also “authorized district courts to rely on extrinsic evidence,” such as technical dictionaries and standard textbooks. *Phillips*, 415 F.3d at 1317. Such references may allow a court “‘to better understand the underlying technology’ and the way in which one of skill in the art might use the claim terms.” *Id.* at 1318 (quoting *Victronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584, n.6 (Fed. Cir. 1996)).

### III. ARGUMENT

Claim Term	Defendants’ Construction	Plaintiffs’ Construction
“pharmaceutically stable”	“without significant change in chemical and physical integrity for pharmaceutical use”	“plain meaning, <i>i.e.</i> , shelf stable for periods greater than 24 months at room temperature”

#### A. Defendants’ Construction For “Pharmaceutically Stable” Is Supported By The Intrinsic Record

The first step in claim construction is to examine the language of the claims themselves. All of the claims of the asserted patents recite a “pharmaceutically stable” formulation of palonosetron. Even though the specification describes “shelf-stable” palonosetron formulations, none of the asserted claims claim “shelf-stable” formulations. Because the specification uses the terms “pharmaceutically stable” and “shelf stable” as independent and distinct properties of the purportedly inventive palonosetron formulations, it is wholly inappropriate for Plaintiffs to advocate for a construction that conflates the terms during this proceeding. As explained below, the term “pharmaceutically stable” should be given its plain and ordinary meaning. There is nothing in the claims to suggest otherwise.

The next step is to determine whether the claim term should be construed consistent with its plain and ordinary meaning, or whether the inventors defined the claim term to have a specific meaning. When the inventors of the asserted patents wanted to define a term in a specific way, they expressly did so in the patent specification. In particular, the patent specification includes a section entitled “Definitions” where particular terms of art, including “vial,” “palonosetron,” “pharmaceutically acceptable,” and “pharmaceutically acceptable salts,” are defined. Ex. 2, ‘724 patent at col. 3, l. 34 – col. 4, l. 39. The specification does not similarly provide an express definition for the term “pharmaceutically stable.” In fact, the inventors did not define “pharmaceutically stable” in any specific way anywhere else in the patent specification, apart from using the term consistent with its plain and ordinary meaning. In light of this, the claim term should be given its plain and ordinary meaning. *See Symantec Corp.*, 522 F.3d at 1291.

The plain and ordinary meaning of “pharmaceutically stable” is “without significant change in chemical and physical integrity for pharmaceutical use,” as provided by the official pharmacopeia of the United States and standard pharmacy textbooks. *See, e.g.*, Ex. 15, United States Pharmacopeia USP 25, General Information, <1151> Pharmaceutical Dosage Forms, 2213-25, 2213 (2002) (describing “stability” in terms of “the ***chemical and physical integrity*** of the dosage unit”) (emphasis added); Ex. 16, Remington: The Science and Practice of Pharmacy, 20<sup>th</sup> Ed., 52:986-994, 986 (2000) (describing “stability” as the ability “to ***remain within its physical, chemical***, microbiological, therapeutic, and toxicological ***specifications***”) (emphasis added). As is supported by evidence in the intrinsic record, the inventors used the term “pharmaceutically stable” in its plain and ordinary sense, *i.e.*, little or no change in physical and chemical integrity.

**1. The Specification Describes “Pharmaceutically Stable” According To A Formulation’s Physical And Chemical Integrity; Not According To Shelf-Life**

The patent specification describes different types of inventions and embodiments of those inventions, as is typical with many patent disclosures. For example, the specification states that one of the objects of the present invention is to provide a palonosetron formulation with “increased pharmaceutical stability,” while another and separate object of the invention is to provide a formulation that “would allow for prolonged storage.” Ex. 2, ‘724 patent at col. 2, ll. 42-52. The specification first describes how using specific excipients in specific concentrations will result in “pharmaceutically stable” palonosetron formulations. *Id.* at col. 4, l. 41 – col. 6, l. 26. Then, the specification separately describes how the “pharmaceutically stable” palonosetron formulations “can be stored or manufactured”: “the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature.” Thus, although there is disclosure of “shelf stability for periods greater than 24 months at room temperature” in the Summary of the Invention (*id.* at col. 2, ll. 59-60), the patent specification does not attribute this shelf-stability requirement to all “pharmaceutically stable” palonosetron formulation embodiments, let alone to the invention that is directed to palonosetron formulations. Instead, such requirement of greater than 24 months at room temperature relates to the “prolonged storage” invention, as discussed in detail below.

Notably, the inventors describe the different inventions of their patent right after they identify “a need for a palonosetron formulation with ***increased stability*** and thereby ***increased shelf life***.” *Id.* at col. 2, ll. 36-37 (emphasis added). Thus, the patent specification itself uses and recognizes the properties of “stability” separately from the properties of “shelf life” and “shelf stability,” and addresses each of these concepts with separate inventions.

The examples of the patent specification plainly show that “pharmaceutically stable” has its plain and ordinary meaning of “without significant change in chemical and physical integrity for pharmaceutical use.” The inventors included seven examples in the patent specification that are related to their so-called inventive formulation. In these examples, the inventors summarize the results of stability studies they conducted on the palonosetron formulations. Where “stability” is described, the inventors focused on the degree of change in the physical and/or chemical integrity of the palonosetron formulation that was studied. *See, e.g., id.* at Examples 1-3 and 6-7; col. 8, ll. 46-48; col. 9, ll. 14-17 (“[a]ll samples were physically stable throughout the study” because the solutions “remained clear, and *little or no change* in particulate burden and haze level were found”) (emphasis added); col. 8, ll. 48-50; col. 9, ll. 17-20 (“*little or no loss* of palonosetron HCl occurred in any of the samples at either temperature throughout the entire study period”) (emphasis added). Nowhere in any of the examples do the inventors conclude or even suggest that the representative formulations are “pharmaceutically stable” because they are shelf-stable for periods greater than 24 months at room temperature. Rather, the longest time period reported in any stability study from the examples of the patent specification is 14 days at 4° C. Thus, the patent specification describes the palonosetron formulations as being “pharmaceutically stable” when there is not a significant change in chemical and physical stability.

## 2. The Inventors Discussed “Pharmaceutically Stable” In Terms Of Degradation And Loss Of Potency During Prosecution

The prosecution history of the asserted patents also supports Defendants’ construction of “pharmaceutically stable.” During prosecution, one of the inventors, Daniele Bonadeo, had to submit a Declaration in order to overcome an Examiner’s rejection of the pending claims over the prior art. Ex. 17, February 9, 2009 Bonadeo Declaration at 1-8. In his Declaration, Mr.

Bonadeo presented data from the “[n]umerous stability studies that have been performed on the injectable formulation of palonosetron over the years to evaluate how changes to the formulation and manufacturing process would impact stability.” *Id.* at ¶ 6. When referring to the stability of the formulations, the stability data was reported as “% degradation” or “% of palonosetron remaining” as a function of a specified time period (*e.g.* days; 1-8 weeks; or 1-6 months). *Id.* at Tables 1-4. These parameters reflect changes in chemical stability of the formulations. The change in chemical stability, or lack thereof, again is consistent with Defendants’ proposal of how “pharmaceutically stable” should be construed. And nowhere in his Declaration did Mr. Bonadeo claim that the formulations were inventive because they were shelf stable for periods greater than 24 months at room temperature.

With respect to the stability data in particular, Table 2 of the Bonadeo Declaration reports the results of a pH-stability study for palonosetron solutions (*see also* Example 1 of the patent specification). *Id.* at ¶¶ 10-11. The study was based on the “T<sub>90</sub>” outcome – the number of days at which 90% of palonosetron remained. While formulations with a pH of 2.0, 7.4, and 10.0 reached a T<sub>90</sub> at 76 days, 180 days, and 270 days, respectively, the formulation with a pH of 5.0 still had 99.2% palonosetron remaining even after 252 days. Based on these numbers, the inventors concluded that the optimal pH where palonosetron is “extremely stable” and “most stable” is at a pH 5.0. Notably, the “stability” of the pH 5.0 palonosetron formulation was judged based on the minimal change in chemical integrity, not on its shelf-life time or temperature. More importantly, “stability” was awarded without ever showing a T<sub>90</sub> past a period of greater than 24 months; instead, the formulation was deemed stable after testing for less than 9 months.

There were also additional admissions by the other inventors (Georgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia, and Riccardo Braglia) that further support Defendants' construction of "pharmaceutically stable." In attempting to overcome an Examiner's rejection of the pending claims over the prior art, the inventors stated:

- 5) This patent application is based on the discovery of liquid formulations of palonosetron with *improved stability*.
- 6) The formulations can be stored for prolonged periods of time in a variety of conditions *without significant degradation or loss of potency*, and thus are considered *pharmaceutically stable*.

Ex. 18, November 21, 2007 Calderari *et al.* Declaration at 2; *see also* Ex. 19, February 13, 2007 Bonadeo Declaration at 1-2 (same). Importantly, where the inventors actually define what they "considered" to be "pharmaceutically stable," they never required that it be "shelf stable for greater than 24 months at room temperature." Rather, the inventors admit that the term "pharmaceutically stable" can encompass a variety of time periods and storage conditions. What is required, however, is that the formulation is "without significant degradation or loss of potency," which is consistent with Defendants' construction.

#### **B. Plaintiff's Construction For "Pharmaceutically Stable" Is Inconsistent With Both The Intrinsic Record And Extrinsic Evidence**

In direct contrast to the teachings of the patent specification and arguments put forth by the inventors during prosecution of the asserted patents, Plaintiffs propose that the term "pharmaceutically stable" means "shelf stable for periods greater than 24 months at room temperature." But as is made clear from the extrinsic evidence cited by both Plaintiffs and Defendants, this construction is at odds with how a person of ordinary skill in the art would have understood this term. At best, Plaintiffs' construction (requiring a shelf stability of greater than 24 months at room temperature) is a preferred embodiment of the claimed invention to

pharmaceutically stable palonosetron formulations, and it is improper to now read such a preferred embodiment into the construction of the claim term “pharmaceutically stable.” *See Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 807 (Fed. Cir. 2007) (dismissing claim construction argument as “an improper attempt to read a feature of the preferred embodiment into the claims as a limitation”). Therefore, for all of the reasons discussed further below, the Court should reject Plaintiffs’ proposal for the term “pharmaceutically stable.”

**1. The Specification Distinguishes Between “Pharmaceutical Stability” And “Shelf Stability”**

The patent specification does not support Plaintiffs’ proposal that the plain and ordinary meaning of “pharmaceutically stable” is “shelf stable for periods greater than 24 months at room temperature.”

*First*, the patent specification describes that “by adjusting the formulation’s pH and/or excipient concentrations, it is possible to increase the stability of palonosetron formulations.” Ex. 2, at col. 3, ll. 7-9; col. 5, ll. 3-5. Similarly, the patent specification describes that “the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations.” *Id.* at col. 3, ll. 22-24; col. 5, ll. 50-52. This is consistent with the scope of the originally filed claims that are directed to the invention of a *pharmaceutically stable solution* comprising palonosetron. Ex. 5, ‘311 Application at 15-20 (*e.g.* claims 1, 32, 42, 51, 53, 56). Importantly, there is nothing in the patent specification that requires that the pharmaceutically stable palonosetron formulations have a shelf life of greater than 24 months at room temperature. The data reported in Examples 1-7 (and the corresponding data submitted in the Bonadeo Declaration during prosecution) underscores this point: none of the tested formulations that are presumably pharmaceutically stable reflect that they have a shelf stability for periods of greater than 24 months at room temperature. Rather, the stable formulations are described in terms of

having a suitable physical and/or chemical stability only after days, weeks, or months. Indeed, Examples 6 and 7 conclude that the palonosetron formulations were stable at 23° C (*i.e.* about room temperature) when tested only after 1, 4, 24, and 48 hours. Ex. 2, ‘724 patent at col. 8, ll. 36-39; col. 9, ll. 4-7.

*Second*, where the patent specification does describe “shelf stability” issues, it is only with respect to embodiments of the invention related to *prolonged storage*. For example, the specification describes that “[s]till further embodiments relate to improvements in the ease with which the palonosetron formulation can be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow ***storage of the product for extended periods of time at room temperature.***” *Id.* at col. 6, ll. 27-32 (emphasis added). In this regard, the specification describes a method of storing a container with a solution of palonosetron in a room “for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months).” *Id.* at col. 6, ll. 39-41. Again, this is consistent with the scope of the originally filed claims that are directed to the invention of a ***method of storing*** a container of palonosetron solution for one month or more (*see* Ex. 5, ‘311 Application at 15-20 (*e.g.* claim 57)), not to the invention of a ***pharmaceutically stable palonosetron formulation*** as Plaintiffs are now trying to suggest. Notably, neither the descriptions for the storage invention in the specification, nor the original claims directed to the storage invention, include the claim term “pharmaceutically stable.” Therefore, based on ample evidence in the patent specification itself, Plaintiffs’ construction should be rejected.

**2. The Inventors Represented To The Patent Office That “Pharmaceutically Stable” Was Separate And Distinct From “Shelf Stability”**

The arguments that the inventors made during prosecution of the asserted patents are also directly inconsistent with the position they are taking now during claim construction. Each of the underlying applications was originally filed with broad claims to pharmaceutically stable palonosetron solutions for reducing emesis. The original claims also included claims directed to other inventions, including a method of storing a container of palonosetron solution for one month or more, and a method for filling a container with a palonosetron solution.

For example, the original claims from the ‘311 application included claims to a “pharmaceutically stable” solution, such as claim 32 (which eventually issued as claim 1 of the ‘724 patent):

32. A pharmaceutically stable solution for preventing or reducing emesis comprising:
- a) from about 0.03 mg/ml to about 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof; and
  - b) a pharmaceutically acceptable carrier.

Ex. 5, ‘311 Application at 15-20.<sup>6</sup> The claims (*e.g.* claim 32) were amended to add a limitation specifying that the “pharmaceutically stable” solutions have a particular “shelf stability”:

32. A pharmaceutically stable solution for ~~preventing or~~ reducing emesis or reducing the likelihood of emesis comprising:
- a) from about 0.03 mg/ml to about 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof; ~~and~~
  - b) a pharmaceutically acceptable carrier; and
  - c) a shelf stability of twelve months or more when stored at greater than about ten degrees celcius.

Ex. 6, February 26, 2007 Amendment at 3-6.<sup>7</sup>

<sup>6</sup> See also Ex. 20, March 24, 2006 ‘268 Application at 15-16; Ex. 21, March 24, 2006 ‘270 Application at 15-16.

<sup>7</sup> See also Ex. 22, February 26, 2007 Amendment in ‘268 Application at 2-4; Ex. 23, February 26, 2007 Amendment in ‘270 Application at 2-4.

The amended claims, however, were rejected as invalid in view of the prior art. Ex. 7, October 5, 2007 Office Action at 6-7.<sup>8</sup> In response, the inventors submitted declarations to overcome the prior art (*see* Exs. 18-19), and then again amended the claims with the “shelf stability” limitation, for example in claim 32, and cancelled all other independent claims:

32. A pharmaceutically stable solution for reducing emesis or reducing the likelihood of emesis comprising:
- a) from ~~about~~ 0.03 mg/ml to ~~about~~ 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, at a pH of from 4.0 to 6.0;
  - b) a pharmaceutically acceptable carrier; and
  - c) a shelf stability of from twelve months to two years ~~or more~~ when stored at ~~greater than about~~ from ten to twenty degrees celcius.

Ex. 26, July 14, 2008 Amendment at 3-4.<sup>9</sup>

Despite these further amendments, the claims that recited a “shelf stability” limitation were still rejected by the Examiner. Ex. 8, October 6, 2008 Office Action at 5-8.<sup>10</sup> The inventors then chose to amend the claims to delete the “shelf stability” limitation and instead replace it with limitations to specific excipients and excipient concentrations of the claimed pharmaceutically stable formulations:

32. A pharmaceutically stable intravenous solution for reducing emesis or reducing the likelihood of emesis comprising:
- a) from 0.03 mg/ml to 0.2 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, buffered at a pH of from 4.0 to 6.0; and
  - b) a pharmaceutically acceptable sterile aqueous carrier including a tonicifying effective amount of mannitol and from 0.005 mg/ml to 1.0 mg/ml EDTA; ~~and~~
  - e) ~~a shelf stability of from twelve months to two years when stored at from ten to twenty degrees celcius.~~

<sup>8</sup> *See also* Ex. 24, October 3, 2007 Office Action in ‘268 Application at 4-6; Ex. 25, September 20, 2007 Office Action in ‘270 Application at 5-6.

<sup>9</sup> *See also* Ex. 27, December 13, 2007 Amendment in ‘268 Application at 2-4; Ex. 28, December 13, 2007 Amendment in ‘270 Application at 3-5.

<sup>10</sup> *See also* Ex. 29, July 15, 2009 Office Action in ‘268 Application at 4-8.

Ex. 9, April 6, 2009 Amendment at 3-4.<sup>11</sup>

The inventors shifted gears and argued that the claimed formulations were now patentable because of the alleged novelty of the recited excipients and excipient concentrations. *Id.* at 5-9; *see also* Ex. 10, May 24, 2010 Appeal Brief.<sup>12</sup> Notably, the inventors abandoned their position that the claims were patentable because of the “shelf stability” limitation. Pending claim 32 issued as independent claim 1 of the ‘724 patent, and none of the issued claims included limitations to a particular shelf stability.

Because the inventors tried, but failed, during prosecution to include an express limitation to a particular shelf stability and storage conditions, they should not be allowed to do so now during claim construction. Specifically, claim 32 of the ‘311 application was narrowed to require “a shelf stability of twelve months or more when stored at greater than about ten degrees celsius.” This limitation covers the same scope as the “shelf stability for periods greater than 24 months at room temperature” construction that Plaintiffs now propose for “pharmaceutically stable.” Importantly, it is clear from the amendments that where applicants wanted to include a shelf stability requirement, they knew how to do so with an express limitation to that effect. *Pass & Seymour, Inc. v. Int’l Trade Com’n*, 617 F.3d 1319, 1324 (Fed. Cir. 2010) (rejecting patentee’s construction because patentee could have written its claim to include additional requirement if it had wanted to).

Moreover, the plain and ordinary meaning of “pharmaceutically stable” cannot mean the same thing as “shelf stability for periods greater than 24 months at room temperature” because if

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<sup>11</sup> *See also* Ex. 11, December 15, 2009 Amendment in ‘268 Application at 2; Ex. 13, April 29, 2009 Amendment in ‘270 Application at 2-4.

<sup>12</sup> *See also* Ex. 11, December 15, 2009 Amendment at 4-16 and Ex. 12 October 11, 2010 Appeal Brief in ‘268 Application; Ex. 13, April 29, 2009 at 5-7 and Ex. 16, November 13, 2009 Appeal Brief in ‘270 Application.

this were the case, then there would have been no reason for the inventors to try to add a separate limitation to the claims that covers this claim scope. Furthermore, claim 32 was further narrowed during prosecution to limit the shelf stability to “*twelve months to two years* when stored at *ten to twenty* degrees Celcius.” But if “pharmaceutically stable” means a shelf life of *greater than 24 months at room temperature* as Plaintiffs now propose, then this would be entirely inconsistent with the claim amendments made by the inventors during prosecution because “greater than 24 months” is outside the range of “twelve months to two years” and “room temperature” is outside the range of “ten to twenty degrees celcius.” For this reason alone, Plaintiffs proposal should be rejected.

The prosecution of the ‘424 patent further supports that “pharmaceutically stable” is not synonymous with “shelf stable for greater than 24 months at room temperature,” as Plaintiffs now argue. In an August 2008 Amendment, independent claims 1 and 11 were pending and both claims were directed to “pharmaceutically stable” palonosetron solutions. Ex. 30, August 25, 2008 Amendment at 2-3. The applicants amended claim 1 to include a shelf stability limitation (“having a shelf stability of from twelve months to two years when stored at from ten to twenty degrees Celcius”), but applicants did not amend claim 11 in the same way. The applicants then explained:

Claim 11 is the only other independent claim and it is identical to claim 1, except that it does not limit the pH of the formulation or require 1-2 year stability (*though it does require a stable formulation*).

*Id.* at 5 (emphasis added).

Later during prosecution of the ‘424 patent, the Examiner confirmed the understanding that the invention to “pharmaceutically stable” palonosetron solutions on the one hand, and the invention to methods of storing palonosetron solutions for greater than 24 months at room

temperature, were separate inventions. In a January 2009 Advisory Action, the Examiner explained:

*[T]he claims are directed to a product as a pharmaceutically stable aqueous solution, versus a method of prolonging stability through storage. Therefore, Applicant's "unexpected" results related to storage are NOT commensurate in scope with the claimed pharmaceutical solution. In other words, the claims are not directed to storing the drug for 2 years prior to use.*

Ex. 31, January 23, 2009 Advisory Action at 3 (emphasis added). Again, based on the abundance of evidence from the intrinsic record, including the prosecution history of the asserted patents, Plaintiffs' proposed construction should be rejected.

### **3. Standard Textbooks And References Provide That "Pharmaceutically Stable" Does Not Require Any Particular Shelf Life**

One of ordinary skill in the art would also understand that "pharmaceutically stable" and "shelf stability" do not have the same meaning, as further confirmed by how these terms are used in standard textbooks and references. For example, the 2002 edition of the United States Pharmacopeia includes a chapter entitled "Pharmaceutical Dosage Forms." In the subsection on stability, the U.S. Pharmacopeia includes the following:

#### **STABILITY**

*The term "stability", with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.*

Ex. 15, U.S. Pharmacopeia at 2213 (emphasis added). In the first sentence, "stability" is defined in terms of "chemical and physical integrity," which is consistent with Defendants' proposed construction. *See supra* at 7. Notably in the next sentence, the U.S. Pharmacopeia separately

defines “shelf life” of the dosage form as a separate concept with a distinct meaning: “the time lapse from initial preparation to the specified expiration date.”

Similarly, the standard textbooks and references, including those cited by Plaintiffs in these proceedings echo the understanding that a person of ordinary skill in the art would define “stability” and “shelf life” separately. The 2000 edition of Remington: The Science and Practice of Pharmacy included a chapter entitled “Stability of Pharmaceutical Products.” The authors provided the following definitions for stability and shelf life:

***Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package.*** These stability data involve selected parameters that, taken together, form the stability profile.

***Stability of a drug also can be defined as the time from the date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.*** Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level. ***Expiration dating then is defined as the time which the preparation will remain stable when stored under recommended conditions.***

Ex. 16, Remington at 986 (emphasis added). Thus, the extrinsic evidence confirms that the plain and ordinary meaning of “pharmaceutically stable” does not mean the same thing as “shelf stability” for a particular time period and under particular storage conditions, as Plaintiffs suggest.

## **CONCLUSION**

For all the above reasons, Defendants respectfully request that the Court construe the claim term “pharmaceutically stable” in the asserted claims of the ‘724, ‘725, and ‘424 patents as proposed by Defendants.

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Respectfully,

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**CERTIFICATE OF SERVICE**

I hereby certify that on May 21, 2012, a true and correct copy of DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF and DECLARATION OF JOVIAL WONG IN SUPPORT OF DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF was served upon all counsel of record via ECF and e-mail.

*s/Michael E. Patunas*  
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